IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

App. No.	:	10/699,511	Confirmation No. 3571
Applicant	:	Bennett, George N.	
Filed	:	October 31, 2003	
TC/A.U.	:	1637	
Examiner	:	Calamita, H.	
Docket No.	:	31175413-002002 (22055)	
Customer No.	:	51738	
Entitled	:	Method for Assembling PCR Fragments of DNA	

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

REPLY BRIEF PURSUANT TO 37 C.F.R. §41.41

The present Reply Brief is in response to the Examiner's Answer of May 29, 2008. The two-month deadline for filing this Reply Brief is July 29, 2008. Thus, this filing is timely.

ARGUMENTS IN RESPONSE TO THE EXAMINER'S ANSWER

In response to the Examiner's Answer, the Appellant submits the following reply arguments. While the below reply arguments only address points argued by the Examiner in the Examiner's Answer, the Appellant continues to assert all of the grounds of patentability set forth in the prior Appeal Brief, as well as advanced during the prosecution of the present application.

I. RESTRICTION ENDONUCLEASES AND LIGASES NOT TOPOLOGICALLY SENSITIVE

The Examiner stated in the Answer that "restriction endonucleases and ligases are also topologically sensitive" (Page 10 of the Answer).

Appellants are unaware of any scientific journal or textbook that considers restriction endonucleases or ligases as "topologically sensitive." Quite on the contrary, restriction endonucleases and ligases are simple enzymes – they recognize the secondary structure[1] (2D) of small nucleotide sequences (often less than 10bp) and cut or link the nucleotide sequences **irrespective** of the **3-dimensional** configuration. Thus, most restriction enzymes, for example, cut supercoiled DNA, nicked circle DNA and linear DNA, as long as the 2D structure matches that recognized by the enzyme. Ligases, join two DNA ends only where they are already held in abutment by annealing, and this the ligase reaction also requires recognition of a 2D nicked DNA structure.

If the Examiner is aware of any scientific journal or textbook illustrating the contrary, the Examiner should provide citations. If the Examiner is relying on personal knowledge, the

[1] Examiner states that "nucleotide specificity" is required for these enzymes. Nucleotide sequence is primary structure, and is a requirement, but double helix or secondary structure is also required for activity, and neither enzyme functions with only primary structure. See http://www-scf.usc.edu/~chem203/resources/DNA/primstruc.html and http://www-scf.usc.edu/~chem203/resources/DNA/secstruct.html. In contrast, "topology" refers to the 3D structure in space.

Examiner should so state in a proper evidentiary form (e.g. a declaration). Mere **arguments** without any factual support are insufficient.

II. RESTRICTION ENDONUCLEASES AND LIGASES NOT TOPOLOGICALLY SENSITIVE TO THE SAME EXTENT AS RECOMBINASE

In the Examiner's Answer, the Examiner further stated that "[b]oth restriction endonucleases and ligases are topologically sensitive **to the same extent** as Cre recombinase." (Pages 6 and 10 of the Answer) (Emphasis added).

Even assuming that restriction endonucleases and ligases possess a minimum level of topological (3D) sensitivity, it is nowhere comparable to that of recombinases. As stated above, restriction endonucleases and ligases are simple enzymes that typically recognize 2D structure. In contrast, recombinases are well known for their ability to catalyze the exchange of nucleotide sequences between **separate DNA strands**, particularly the exchange of homologous regions between the paired maternal and paternal **chromosomes**. The 3D complexity of this reaction and the knots that are part of the reaction are far beyond that of restriction endonucleases and ligases. This contradicts directly with the Examiner's argument that "[b]oth restriction endonucleases and ligases are topologically sensitive **to the same extent** as Cre recombinase."

III. INVENTOR'S DECLARATION IMPROPERLY DISMISSED

In the Examiner's Answer, the Examiner stated that the Declaration submitted by an inventor of the current application, Dr. Bennett, merely represents the opinion of Dr. Bennett, not a fact. (Page 11 of the Answer ("This prediction is merely the opinion of Dr. Bennett, not a fact.")) The Examiner further stated that, in the absence of evidence showing that binding DNA to a solid substrate the structure is changed so markedly that recombinase would not function, Dr. Bennett's Declaration is not persuasive because it was not supported by **any evidence**

showing this effect (Page 12 of the Answer). The Examiner's assertions are wrong both in law and in logic.

Dr. Bennet's opinion was supported at least by the five (5) scientific journal articles listed in Appendix B of the Appeal Brief of the current application. On the contrary, the Examiner did **not** cite any reference to rebut Dr. Bennet's Declaration. The predecessor court of the Federal Circuit has held that expert testimonies based on documentary supports are sufficient to overcome a *prima facie* case of obviousness. *In re Oelrich*, 579 F.2d 86, 198 USPQ 210 (CCPA 1978); see also *In re Carroll*, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979) (expert opinion on what the prior art taught, supported by documentary evidence, must be considered with deferential weight).

The Examiner's statement is also logically wrong. It equates the concept of "**sufficient** proof" with "**necessary** proof." In the absence of evidence showing that binding DNA to a solid substrate the structure is changed so markedly that recombinase would not function, there could still be evidence supporting Dr. Bennett's position that at the time of the invention there was no reasonable expectation of success. A negative example would be **sufficient** (indeed, it would be a "teaching away" reference), but it is by no means the only type of evidence that is **necessary** to prove Dr. Bennett's position. As long as people skilled in the art (such as Dr. Bennett) do not expect the claimed invention would succeed, an actual negative experiment is not required.

Accordingly, Appellants repeat that Dr. Bennet's Declaration is properly supported by documentary evidence, and must be afforded with proper weight when evaluating the patentability of the current application.

IV. NO EVIDENCE PROVIDED BY EXAMINER

Throughout the Examiner's Answer, the Examiner has been arguing based on personal knowledge and speculations, without citation or factual support. Despite Applicants/Appellants'

repeated requests that the Examiner provide a declaration under the penalty of law to support her position in the proper evidentiary form, the Examiner still refuses.

The law is clear – "it is impermissible for the Board to base its factual findings on **its expertise**, rather than on **evidence** in the record." *Brand v. Miller*, 487 F.3d 862, 868-69 (Fed. Cir. 2007) (emphases added). **Personal knowledge** is not competent evidence in prosecution and on appeal. *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993). Accordingly, Appellants submit that, based on the evidence in the record, the Examiner's position must be rejected as a matter of law.

CONCLUSIONS

In summary, the Examiner's Answer is not supported by evidence, contains arguments erroneous in law and in logic, and is based on improper speculations and assumptions. Therefore, the final rejections imposed by the Examiner on the current application should be reversed.

If any questions or issues remain in the resolution of which the Board feels will be advanced by a conference with the Applicants' attorney, the Board is invited to contact the attorney at the number noted below. No fees are believed to be due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420 (reference 31175413-002002 Valoir).

Dated: July 28, 2008

Respectfully submitted,

BAKER & MCKENZIE LLP

By /Tamsen Valoir/

Tamsen Valoir, PhD
Registration No.: 41,417
Pennzoil Place, South Tower
711 Louisiana, Suite 3400
Houston, Texas 77002-2746 USA
Tel: +1 713 427 5007
Fax: +1 713 427 5099
Email: Tamsen.Valoir@bakernet.com
Attorneys For Applicants